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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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MEMORANDUM

SUBJECT: Proposed two-year rat feeding study with linuron; Caswell 528; EPA I.D. # 035506; Project 7-0131; Record No. 183734

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and
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and
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12/11/86

ACTION: Review of proposed two-year rat feeding study with linuron; Caswell 528; EPA I.D. # 035506; Project 7-0131; Record No. 183734

RECOMMENDATIONS:

It is not the policy of the Toxicology Branch to review general chronic study protocols. For general requirements, the registrant is referred to § 83-5, pages 137-146 of the FIFRA Pesticide Assessment Guidelines, Subdivision F. However, the dose level requirements and the method of blood pigment analysis require some comment since they have been raised as issues in regard to data gaps and to previously submitted data (rat blood pigment study).

The registrant has not proposed dose levels for the study. It should be noted that in the rat study performed by Kaplan(1980) a possible effect level (LEL) at 50 ppm for abnormal hematology was suggested. Therefore, in order to be assured of establishing a no-observed effect level (NOEL) in the proposed study, the low dose level should probably be below the LEL previously observed.

The method for the analysis of blood pigments has been recently reviewed by the EPA in a separate discussion on industry rebuttal comments (see review of linuron rebuttal comments on met- and sulfhemoglobin; EPA I.D. # 035506). EPA considers the method described in that submission to be appropriate for the

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measurement of methemoglobin and sulfhemoglobin. It is recognized, from the difficulties encountered in the rat study in measuring small percent conversions (1-2%) of total hemoglobin to sulfhemoglobin, that the sensitivity of the method may not allow small changes in blood pigments to be evaluated.

Other suggestions are given below for the registrant's consideration:

1. GLP considerations

As per the EPA Good Laboratory Practices, the protocol should make provision for the determination of the stability of the stock test substance, i.e., in addition to its stability and concentration in the feed mixture [see § 160.105(e)]. In addition, for studies of more than 4 weeks' duration, reserve samples from each batch of test and control subtances must be retained for the period of time provided by §160.195 [see § 160.105 (d)].

2. Other comments (as per the 1982 FIFRA Pesticide Assessment Guidelines)

- clinical chemistry: chloride, magnesium, phosphorus, creatinine phosphokinase should be included
- urine analysis: specific gravity should be included
- histopathology: the gall bladder should be evaluated

NOTE: The registrant is advised not to commence the chronic rat study until the issues concerning the statistical re-analysis of the Kaplan (1980) study have been resolved, at which time it may be determined that a new study is not appropriate (see EPA review of statistical re-analysis of rat hematology data)